REMARKS

This Amendment is submitted in response to the November 20, 2000 Office Action. Upon entry of the above amendments, claims 2-4, 8-10, 12-14, 18, and 25 will be pending in this application.

Applicant in the present Amendment has canceled the claims to pharmaceutical compositions and methods of use, namely claims 21, 22, 23, and 24, in order to advance the prosecution of the subject application. Applicant has also amended claims 18 and 25, however such amendments do not raise an issue of new matter, as is discussed below. Thus, applicant maintains that the amendments do not raise an issue of new matter. Applicant will file a divisional patent application to pursue claims 21, 22, 23, and 24 claiming priority of the subject application.

In the November 20, 2000 Office Action, the Examiner argued that the term "these moieties" in claim 18, as seen in line 4 of page 4 of applicant's October 20, 2000 Preliminary Amendment, is not clear. It is clear, however, from the specification and original claim 1 that the term "these moieties" refers to both the (C_1-C_4 alkyl) and the (C_1-C_6 alkyl) groups of the R_4 options. Note that original claim 1 states "wherein each of the (C_1-C_6 alkyl and (C_1-C_4 alkyl) moieties in the foregoing R_4 groups may optionally contain one or two double or triple bonds and may optionally be substituted with one or two substituents . . ." (see page 50, lines 17-19, of the specification of the subject application). Accordingly, applicant has above provided a new claim 18, wherein said term "these moieties" has been replaced with the phrase "said (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties". Applicant kindly requests that the Examiner withdraw the rejection under 35 USC 112, second paragraph, of claim 18 because of the term "these moieties".

The Examiner also objected to the term "R^{12}" in claim 18 (referring to page 4, line 13, of applicant's Preliminary Amendment), noting that the term in unnecessary and its presence does not affect the scope of the claim. Accordingly, applicant has deleted "R^{12}" from above replacement claim 18. Applicant kindly requests that the Examiner withdraw the objection to claim 18 based on the "R^{12}" term.

The Examiner also argued that the -NR^1R^2/–$CR^1R^2R^{10}$ ring described in claim 18 on page 3, lines 21-26 of applicant's October 10, 2000 Preliminary Amendment, is unclear. According to the Examiner, since the ring is described as "saturated" it cannot "optionally contain from one to three double ". Accordingly, applicant has in above new claim 18 removed

the term "saturated", instead recited that the ring consists of single bonds and that from one to three of the single bonds of said ring that are carbon-carbon or carbon-nitrogen single bonds may each optionally be replaced with a double bonds. Applicant respectfully requests that the Examiner withdraw the rejection of claim 18 based on description of the -NR^1R^2/–$CR^1R^2R^{10}$ ring therein as "saturated" in light of the new claim 18 above which does not use the term "saturated".

The Examiner also argued that the description of said -NR^1R^2/–$CR^1R^2R^{10}$ ring is also unclear because it at one point refers to the ring "containing a single heteroatom" and at a later point indicates that one or two ring carbon atoms may option ally and independently be replaced by an oxygen or sulfur atom or an –NZ^3 group. The Examiner furthermore noted that the description of said ring is at one point "carbocyclic" and at a later point providing for optional inclusion of heteroatoms. In view of the Examiner's remarks, applicant has deleted from the description of said -NR^1R^2/–$CR^1R^2R^{10}$ ring in above replacement claim 18 the statement that (paraphrasing slightly) "in the case of –$CR^1R^2R^{10}$ the ring is carbocyclic, and in the case of –NR1R2 the ring contains a singly heteroatom, nitrogen". This phrase seems superfluous, and its removal obviates the inconsistencies noted by the Examiner. Applicant kindly requests that the Examiner withdraw his objection to claim 18 regarding the asserted inconsistencies between "carbocyclic" and the inclusion of optional heteroatoms and use of the phrase "a single heteroatom" in light of replacement claim 18 above.

In replacement claim 18 above, applicant has not included the word "either" from the sixth line below the formula I on page 2 of the October 10, 2000 Preliminary Amendment, as the Examiner correctly pointed out in the November 20, 2000 Office Action that the word is unnecessary.

Likewise, the phrase "when it is single bonded to E" (referring to moiety "F") in the seventh line below the formula I on page 2 of the Preliminary Amendment and the phrase "or F" (referring to moieties double bonded to moiety "E") in the fourteenth line below the formula I on page 2 of the Preliminary Amendment have been deleted from claim 18, as the Examiner has correctly noted that F and E, as depicted in formula I, are always singly bonded to one another.

In view of the above, applicant respectfully requests that the Examiner reconsider and withdraw the rejections made to claim 18 under 35 USC 112, second paragraph.

Applicant has also provided above a new replacement claim 25, in which all of the amendments to claim 18 described above have also been made. In replacement claim 25, applicant has furthemore removed "oxygen, sulfur" for moiety "F" as the current claims are intended to be limited to the elected subject matter. Applicant reserves the right to file one or more divisional patent applications to compounds of formula I wherein F is oxygen or sulfur.

The Examiner also maintained that replacement of the term "thioalkyl" with "alkylthio" as in "wherein one or two of the carbon-carbon single bonds in each of the (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties in the foregoin R_4 groups may . . . optionally be substituted with one or two substituents independently selected from . . . C_1-C_3 alkylthio . . ." recited in claims 18 and 25 is new matter. The Examiner on this allegation rejected claims including "alkylthio" under 35 USC 112, first paragraph. The Examiner maintained that there is no way of telling whether "alkylthio" or "mercaptoalkyl" (i.e. "alkylthio") is what was originally intended by "thioalkyl". In the Preliminary Amendment dated October 10, 2000 applicant argued that since none of the other substituents in the list of substituents that may optionally be attached to the (C_1-C_4 alkyl) or (C_1-C_6 alkyl) groups of R_4, then if mercaptoalkyl had been intended it would have simply been incorporated into the (C_1-C_4 alkyl) and (C_1-C_6 alkyl) groups. The Examiner has correctly pointed out, however, that "incorporation" would not have made sense since the (C_1-C_4 alkyl) and (C_1-C_6 alkyl) groups can be substituted by one or two groups that may be the same or different and that include but are not limited to C_1-C_3 alkylthio. Applicant concedes that the argument in the Preliminary Amendment therefore does not make sense. Nonetheless, applicant maintains that C_1-C_3 alkylthio was what was intended when applicant recited "C_1-C_3 thioalkyl" in the originally-filed specification. Moreover, applicant still maintains that since the originally-filed specification recited "C_1-C_3 alkoxy" in the same group of moieties, it would make sense that "C_1-C_3 alkylthio", the homologue to C_1-C_3 alkoxy was clearly what was intended by "C_1-C_3 thioalkyl". Therefore, replacement of C_1-C_3 thioalkyl with C_1-C_3 alkylthio does not constitute new matter. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims under 35 USC 112, first paragraph, for use of the term "alkylthio".

The Examiner also rejected under 35 USC 112, first paragraph, claims which include the moiety R^5 being pyrimidyl substituted by "two or three" substituents and R^5 being phenyl or pyridyl substituted by "two or three substituents further selected from (C_1-C_4 alkyl)O(C_1-C_4 alkyl), OCF_3, and fluoro, and one carbon-carbon single bond of each (C_1-C_4) alkyl group of said

substituents having between two and four carbon atoms may be optionally replaced with a carbon-carbon double or triple bond". This is recited in previous claim 18. The Examiner asserted that the language on page 9 of the specification which provides for R^5 being pyrimidyl or phenyl or pyridyl with additional possible substituents only permits "two or more" substituents on R^5. Accordingly, applicant has in new claim 18 above recited "three" substituents on R^5 when R^5 is pyrimidyl or when R^5 is the phenyl or pyridyl with the further possible substituents.

The Examiner again maintained that inclusion in claim 18 of the term "trifluoromethyl" for R^4 is new matter. Applicant traverses. It is clear from the specification that R^4 includes trifluoromethyl, since it is included as a possibility for R4 on page 9, line 11. The Examiner has asserted that a semicolon means "and", not "or". Since when does a semicolon necessarily mean "and"? The fact is that the clauses separated by semicolons can be read as alternative independent embodiments of the invention. Moreover, it is clear that each clause is intended to represent a narrower selection of substituents. Even if the clauses are read as a combination, as the Examiner has asserted (i.e. read together as a single separate embodiment of the invention), from where is one to obtain the elements "A", "B", etc.? They are obtained by reference back to the genus initially recited starting on page 2 of the specification. Therefore, it is clear that the groups listed for, e.g., R^4 on page 9 of the specification are meant to be narrower groups than the list of possible moieties provided in the initial genus recited starting on page 2, and therefore that "trifluoromethyl" is meant as included for R4 in the initial genus starting on page 2 of the original specification. Thus, as a whole, it appears clear that inclusion of "trifluoromethyl" for R^4 in claims 18 and 25 is not new matter. Applicant respectfully requests that the Examiner reconsider and withdraw his rejection based on listing trifluoromethyl for R^4 in claim 18.

The remainder of the rejections set forth by the Examiner in the November 20, 2000 Office Action are obviated by cancellation herein of the claims directed to pharmaceutical compositions and methods of use. These rejections will be responded to by applicant in the divisional application directed to the compositions and uses, if they are raised.

In conclusion, applicant maintains that the claims as amended herein are clear and are supported by the originally-filed specification. Accordingly, applicant submits that the claims are in condition for allowance. Applicant respectfully requests the earliest possible notification of allowable subject matter.

If a telephone interview would be of assistance in advancing prosecution of this application, the Examiner is invited to telephone applicant's attorney at the telephone number below.

No fee is believed necessary for filing this Amendment, other than the fee for the three month extension of time authorized in the Petition filed concurrently herewith. However, if any other fee is found necessary in connection with filing this Amendment, authorization is hereby given to charge such fee to Deposit Account No. 16-1445.

Respectfully submitted,

Date: May 21, 2001

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APPENDIX A

Attorney Docket Number PC9230C

U.S. Serial No. 08/764,110

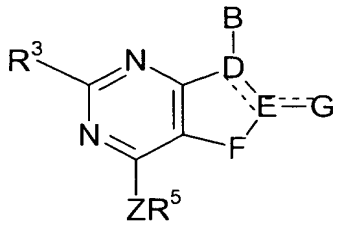
VERSION WITH MARKINGS TO SHOW CHANGES - DO NOT ENTER:

The claims of the above-indicated patent application are amended in the Amendment in response to the November 20, 2000 Office Action, to which this Appendix A is attached as follows:

In the Claims:

Claims 18 and 25 are amended as follows:

18. (Three-times amended) A compound of the formula



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wherein the dashed lines represent optional double bonds;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

E is nitrogen, CH or carbon;

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is ~~either~~ double bonded to E, or D is CH and is single bonded to E;

F is CHR^4 or NR^4 ~~when it is single bonded to E~~; provided that at least one of D and E is nitrogen or F is NR^4 , and provided that only one of D and E is nitrogen, and D and E are not nitrogen when F is NR^4;

G, when single bonded to E, is hydrogen, C_1-C_4 alkyl, -S(C_1-C_4 alkyl), -O(C_1-C_4 alkyl), NH_2, -NH(C_1-C_4 alkyl) or -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), wherein each of the C_1-C_4 alkyl groups of G may optionally be substituted with one hydroxy, -O(C_1-C_2 alkyl) or fluoro

group; and G, when double bonded to E, is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D ~~or E~~, is absent;

R^1 is hydrogen, C_1-C_6 alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, -C(=O)O-(C_1-C_4)alkyl, -OC(=O)(C_1-C_4 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein a carbon-carbon single bond of each of the C_1-C_4 alkyl groups in the foregoing R^1 groups having at least two carbons may optionally be replaced with a carbon-carbon double or triple bond, and one or two carbon-carbon single bonds of each of the C_1-C_4 alkyl groups in the foregoing R^1 groups having four carbons may optionally be replaced with a carbon-carbon double or triple bond; R^2 is C_1-C_{12} alkyl wherein one carbon-carbon single bond of any said alkyl having at least two carbons, one or two carbon-carbon single bonds of any said alkyl having at least four carbons, and from one to three carbon-carbon single bonds of any said alkyl having at least six carbons may optionally be replaced with a carbon-carbon double or triple bond, or R^2 is aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; or R^2 is C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4

alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl);

-NR^1R^2 or -$CR^1R^2R^{10}$ may form a ~~saturated~~ 3 to 8 membered ring consisting of single bonds, ~~that, in the case of -$CR^1R^2R^{10}$, is carbocyclic, and that, in the case of -NR^1R^2, contains a single heteroatom, nitrogen, which ring may optionally contain from one to three double bonds, and~~ wherein one or two of the ring carbon atoms of such a 5 to 8 membered ring may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, and wherein from one to three of the single bonds of such a 3 to 8 membered ring that are carbon-carbon or carbon-nitrogen single bonds may each optionally be replaced with a double bond;

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, -CN, -S(C_1-C_4 alkyl) or -SO_2(C_1-C_4 alkyl) wherein each of the (C_1-C_4 alkyl) moieties in the foregoing R^3 groups may optionally be substituted with one substituent R^9 selected from hydroxy, fluoro and (C_1-C_2 alkoxy);

each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, cyano, amino, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4)alkyl, -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl), wherein one or two of the carbon-carbon single bonds in each of the (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties in the foregoing R^4 groups may optionally be replaced with a carbon-carbon double or triple bond and wherein each of ~~these~~ said (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties may optionally be substituted with one or two substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, methylamino, ethylamino, -NHC(=O)CH_3, fluoro, chloro, C_1-C_3 alkylthio, -CN, -COOH, -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl) and -NO_2;

R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl,

benzoxazolyl or C_3-C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein Z^4 is hydrogen, C_1-C_4 alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents ~~R^{12}~~ wherein one to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl and -O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, -CN, $-CF_3$, $-NO_2$, $-NH_2$, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, $-SO_2$NH(C_1-C_4 alkyl), $-SO_2$N(C_1-C_2 alkyl)(C_1-C_4 alkyl), $-SO_2NH_2$, $-NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and $-SO_2$(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl; and furthermore wherein when R^5 is phenyl or pyridyl substituted with ~~two or~~ three substituents, said substituents can further be selected from (C_1-C_4 alkyl)O(C_1-C_4 alkyl), OCF_3, and fluoro, and one carbon-carbon single bond of each (C_1-C_4) alkyl group of said substituents having between two and four carbon atoms may be optionally replaced with a carbon-carbon double or triple bond; or R^5 is pyrimidyl substituted by ~~two or~~ three substituents independently selected from C_1-C_4 alkyl, -O(C_1-C_4 alkyl), CF_3, OCF_3, -CHO, (C_1-C_4 alkyl)-OH, CN, Cl, F, Br, I and NO_2, wherein a carbon-carbon single bond of said (C_1-C_4) alkyl groups having between two and four carbon atoms may optionally be replaced by a carbon-carbon double or triple bond;

R^7 is hydrogen, C_1-C_4 alkyl, halo, cyano, hydroxy, -O(C_1-C_4 alkyl) -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4alkyl), $-OCF_3$, $-CF_3$, $-CH_2OH$, $-CH_2$O(C_1-C_4 alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

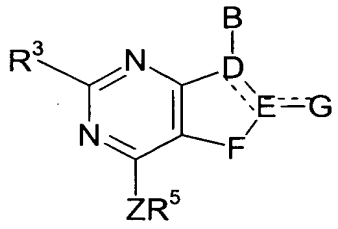
R^{11} is hydrogen or C_1-C_4 alkyl; and

with the proviso that: (a) when R^4 is attached to nitrogen, it is not halo, cyano or nitro; and (b) one of E, D and F must be nitrogen or substituted nitrogen, and only one of E, D and F can be nitrogen or substituted nitrogen;

Z is NH, oxygen, sulfur, $-N(C_1-C_4$ alkyl), $-NC(=O)(C_1-C_2$ alkyl), $NC(=O)O(C_1-C_2$alkyl) or $CR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14} can be cyano;

or a pharmaceutically acceptable salt of such compound.

25. (Once amended) A compound of the formula



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wherein the dashed lines represent optional double bonds;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

E is nitrogen, CH or carbon;

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is ~~either~~ double bonded to E, or D is CH and is single bonded to E;

F is ~~oxygen, sulfur,~~ CHR^4 or NR^4 ~~when it is single bonded to E~~; provided that at least one of D and E is nitrogen or F is NR^4, and provided that only one of D and E is nitrogen, and D and E are not nitrogen when F is NR^4;

G, when single bonded to E, is hydrogen, C_1-C_4 alkyl, $-S(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), NH_2, $-NH(C_1-C_4$ alkyl) or $-N(C_1-C_2$ alkyl)$(C_1-C_4$ alkyl), wherein each of the C_1-C_4 alkyl groups of G may optionally be substituted with one hydroxy, $-O(C_1-C_2$ alkyl) or fluoro group; and G, when double bonded to E, is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D ~~or F~~, is absent;

R^1 is hydrogen, C_1-C_6 alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, $-C(=O)O-(C_1-C_4)$alkyl, $-OC(=O)(C_1-C_4$ alkyl), $-OC(=O)N(C_1-C_4$ alkyl)$(C_1-C_2$ alkyl), $-NHCO(C_1-C_4$

alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein a carbon-carbon single bond of each of the C_1-C_4 alkyl groups in the foregoing R^1 groups having at least two carbons may optionally be replaced with a carbon-carbon double or triple bond, and one or two carbon-carbon single bonds of each of the C_1-C_4 alkyl groups in the foregoing R^1 groups having four carbons may optionally be replaced with a carbon-carbon double or triple bond; R^2 is C_1-C_{12} alkyl wherein one carbon-carbon single bond of any said alkyl having at least two carbons, one or two carbon-carbon single bonds of any said alkyl having at least four carbons, and from one to three carbon-carbon single bonds of any said alkyl having at least six carbons may optionally be replaced with a carbon-carbon double or triple bond, or R^2 is aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; or R^2 is C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), -OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl);

-NR^1R^2 or -$CR^1R^2R^{10}$ may form a ~~saturated~~ 3 to 8 membered ring consisting of single bonds, ~~that, in the case of -$CR^1R^2R^{10}$, is~~

~~carbocyclic, and that, in the case of $-NR^1R^2$, contains a single heteroatom, nitrogen, which ring may optionally contain from one to three double bonds, and~~ wherein one or two of the ring carbon atoms of such a 5 to 8 membered ring may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, and wherein from one to three of the single bonds of such a 3 to 8 membered ring that are carbon-carbon or carbon-nitrogen single bonds may each optionally be replaced with a double bond;

R^3 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, -CN, -S(C_1-C_4 alkyl) or -SO_2(C_1-C_4 alkyl) wherein each of the (C_1-C_4 alkyl) moieties in the foregoing R^3 groups may optionally be substituted with one substituent R^9 selected from hydroxy, fluoro and (C_1-C_2 alkoxy);

each R^4 is, independently, hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, cyano, amino, nitro, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4)alkyl, -CO(C_1-C_4 alkyl), -C(=O)H or -C(=O)O(C_1-C_4alkyl), wherein one or two of the carbon-carbon single bonds in each of the (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties in the foregoing R^4 groups may optionally be replaced with a carbon-carbon double or triple bond and wherein each of ~~these~~ said (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties may optionally be substituted with one or two substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, methylamino, ethylamino, -NHC(=O)CH_3, fluoro, chloro, C_1-C_3 alkylthio, -CN, -COOH, -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl) and -NO_2;

R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C_3-C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein Z^4 is hydrogen, C_1-C_4 alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents ~~R^{12}~~ wherein one to three of said substituents may

be selected, independently, from chloro, C_1-C_6 alkyl and -O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, -CN, $-CF_3$, $-NO_2$, $-NH_2$, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, $-SO_2NH$(C_1-C_4 alkyl), $-SO_2N$(C_1-C_2 alkyl)(C_1-C_4 alkyl), $-SO_2NH_2$, $-NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and $-SO_2$(C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, C_1-C_4 alkyl, halo, cyano, hydroxy, -O(C_1-C_4 alkyl) -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4alkyl), $-OCF_3$, $-CF_3$, $-CH_2OH$, $-CH_2O$(C_1-C_4 alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1-C_4 alkyl; and

with the proviso that: (a) when R^4 is attached to nitrogen, it is not halo, cyano or nitro; and (b) one of E, D and F must be nitrogen or substituted nitrogen, and only one of E, D and F can be nitrogen or substituted nitrogen;

Z is NH, oxygen, sulfur, -N(C_1-C_4 alkyl), -NC(=O)(C_1-C_2 alkyl), NC(=O)O(C_1-C_2alkyl) or $CR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14} can be cyano;

or a pharmaceutically acceptable salt of such compound.